> The two-fold administration of active compound simulated by the fixed or free combination leads in a relatively large space of time (compared with the same dose of active compound as a single administration) to a smaller width of variation in the active compound blood levels in the patients and moreover to more rapid symptom relief.

Applicants enclose a simulated release profile for a combination of an enteric coated form and a sustained release coated form after reaching the intestine to facilitate better understanding of the invention.

In connection with the term "which is customary *per se* for sustained release compositions" attention is respectfully directed to page 3 of the instant specification, starting with the third complete paragraph, which provides an explanation of what is understood by this term.

Applicants submit that the references cited by the Examiner do not suggest all features of the administration form according to their invention based on (1) an enteric coated form and (2) a non-enteric coated form, which has a coating which is customary *per se* for sustained release compositions, which only releases the benzimidazole after gastric passage.

To illustrate the difference in effect between plural delayed release (enteric-coated) formulations and a combination of a delayed release and a sustained release formulation, please find herewith a simulated release profile of the several forms called for by Applicants' claims. Such a difference in release patterns is not achieved by plural enteric-coated compositions.

For further understanding of the nature of pantoprazole, reference is respectfully made to "Physicians' Desk Reference," 56th Ed., pages 3577 and 3578 (copy herewith), 2002.

As is readily appreciated, the release of active compounds according to Applicants' claimed invention is not at "two different points of time" as suggested; release of one formulation is at a

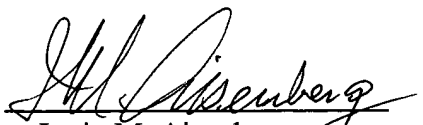
particular point in time, whereas release of the other required composition is over a longer period of time. There is thus a clear difference which is not achieved by applied art.

Issue is respectfully taken with the interpretation of "which is customary *per se* for sustained release compositions"; claims are directed to those of at least ordinary skill in the art, and a noted interpretation is one that would not be taken by such a person. Please note also that each claim of a patent constitutes a separate invention and gives rise to separate rights. *Jones v. Hardy*, 727 F.2d 1524, 1528, 220 USPQ 1021 (Fed. Cir. 1984); *Cyrix Corp. v. Intel Corp.*, 846 F.Supp. 522, 32 USPQ2d 1890, 1901 (TEX 1994).

Pyridin-2-ylmethylsulfinyl-1H-benzimidazoles have their own peculiar properties and limitations. The applied prior art provides no motivation to combine any particular limitations disclosed in the applied art. At the very most, one could fabricate an "obviousness to try." The nature of involved active components, however, is one that even that might be regarded as being far fetched.

Favorable reconsideration and allowance of all of Applicants' claims are in order and are respectfully solicited.

Respectfully submitted,
JACOBSON HOLMAN PLLC

By: 
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milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **RISKS OF ESTROGENS AND/OR PROGESTINS**).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health-care provider.

RISKS OF ESTROGENS AND/OR PROGESTINS

Cancer of the uterus. If you use any drug which contains estrogen, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

The risk of cancer of the uterus increases when estrogens are used alone, the longer they are used, and when larger doses are taken. There is a higher risk of cancer of the uterus if you are overweight, diabetic, or have high blood pressure. The hormone combination you will be taking contains estrogen and progestin. This combination has been shown to provide the benefits of estrogen replacement therapy for the **USES OF ESTROGEN** listed above, while reducing the risk of a pre-cancerous condition of the uterine lining (see **OTHER INFORMATION,** below).

However, additional risks may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include less favorable effects on blood fats as compared to Premarin alone, unfavorable effects on blood sugars, and a possible increase in breast cancer risk (see *Cancer of the breast*, below). Usually, the smaller the dose and the shorter the duration of treatment, the more these effects are minimized. Check with your doctor to make sure you are using the lowest effective dose and only for as long as you need it.

If you have had your uterus removed, there is no risk of developing cancer of the uterus and no benefit to be gained by using a combination estrogen/progestin product.

Cancer of the breast. Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used high doses for shorter time periods. The effects of added progestin on the risk of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone. Others have not. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Regular mammograms are recommended for all women over 40 years of age.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Inflammation of the Pancreas. Women with high triglyceride levels may have an increased risk of developing inflammation of the pancreas.

Abnormal blood clotting. Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (cutting off blood to the brain), a heart attack (cutting off blood to the heart), a pulmonary embolus (cutting off blood to the lungs), retinal thrombosis (cutting off blood vessels in the eye), or other problems. Any of these conditions may cause death or serious long-term disability.

Heart Disease. A recent 4-year study suggests that women with a history of coronary heart disease may have an increased risk of serious cardiac events during the first year of treatment with estrogen/progestin therapy. Therefore, if you have had a heart attack, or you have been told you have blocked coronary arteries (arteries to your heart) or have any heart problem, you should consult your physician regarding the potential benefits and risks of estrogen/progestin therapy.

Excess calcium in the blood. Taking estrogens may lead to severe hypercalcemia in women with breast and/or bone cancer.

During pregnancy. There is an increased risk of birth defects in children whose mothers take this drug during the first four months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses. However, enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy. These drugs have been used as a test for pregnancy, but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available. If you take PREMPRO (conjugated estrogens/medroxyprogesterone acetate tablets) or PREMPHASE (conjugated estrogens/medroxyprogesterone acetate tablets) and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

SIDE EFFECTS WITH ESTROGENS AND/OR PROGESTINS

In addition to the risks listed above, the following side effects have been reported with estrogen and/or progestin use:

- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Yellowing of the skin and/or whites of the eyes.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Irregular bleeding or spotting.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes.
- Worsening of porphyria.
- Headache, migraines, dizziness, faintness, or changes in vision (including intolerance to contact lenses).
- Mental depression.
- Involuntary muscle spasms.
- Hair loss or abnormal hairiness.
- Increase or decrease in weight.
- Changes in sex drive.
- Possible changes in blood sugar.

REDUCING THE RISKS OF ESTROGEN/PROGESTIN

If you decide to take an estrogen/progestin combination, you can reduce your risks by carefully monitoring your treatment.

See your doctor regularly. While you are taking PREMPRO or PREMPHASE, it is important to visit your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast X-ray), you may need to have more frequent breast examinations.

Reassess your need for treatment. You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble. If any of these warning signals (or any other unusual symptoms) happen while you are using estrogen/progestin, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine abnormality).
- Pains in the calves or chest, a sudden shortness of breath or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicating possible clots in the brain or eye).
- Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly).
- Yellowing of the skin and/or whites of the eyes (possible liver problems).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormonal drug, with estrogens lowers the risk of developing this condition. Therefore, since your uterus has not been removed, your doctor has prescribed PREMPRO or PREMPHASE, which includes both a progestin and estrogens.

   You should know, however, that taking estrogens *with* progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse. Additional risks include a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

   Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

   You are cautioned to discuss very carefully with your doctor or health-care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.
2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.
4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center immediately.
5. This leaflet provides the most important information about PREMPRO and PREMPHASE. If you want to read more, ask your doctor or pharmacist to let you read the professional labeling. The professional labeling is also published in a book called *The Physician's Desk Reference*, which is available in bookstores and public

HOW SUPPLIED

PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) is a combination of the conjugated estrogens found in Premarin® tablets and medroxyprogesterone acetate (MPA). Depending on the dosage strength, PREMPRO™ therapy consists of either a single peach tablet or a single light-blue tablet to be taken once daily.

PREMPRO 0.625 mg/2.5 mg

Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg

Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO™ tablets is a trademark of Wyeth-Ayerst Laboratories.

PREMPHASE® (conjugated estrogens/medroxyprogesterone acetate tablets) is a combination of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28. Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 14 oval, maroon Premarin® tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin® tablets and 5 mg of medroxyprogesterone acetate (MPA) for oral administration.

The appearance of Premarin® tablets is a trademark of Wyeth-Ayerst Laboratories. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Keep out of reach of children.

Store at controlled room temperature 20°C–25°C (68°F–77°F).

U.S. Patent Nos. 5,547,948; 5,210,081; Re. 36,247

Manufactured by:
Ayerst Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

CI 6096-3 Revised July 23, 2001

Shown in Product Identification Guide, page 341

PROTONIX®

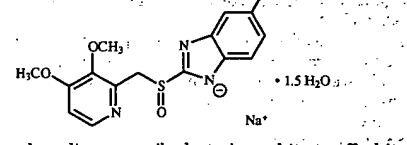
℞

[prō 'tŏn-ĭks]

(pantoprazole sodium)
Delayed-Release Tablets

DESCRIPTION

The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX is supplied as a delayed-release tablet for oral administration. Each delayed-release tablet contains 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg pantoprazole) with the following inactive ingredients: anhydrous sodium carbonate NF, mannitol USP, crospovidone NF, povidone USP, calcium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, yellow iron oxide NF, propylene glycol USP, methacrylic acid copolymer NF, polysorbate 80 NF, sodium lauryl sulfate NF, and triethyl citrate NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Protonix is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

Continued on next page

Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.4 µg/mL, the time to reach the peak concentration (t_{max}) is 2.4 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg•hr/mL. When pantoprazole is given with food, its t_{max} is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6–14.0 L/h and its apparent volume of distribution is 11.0–23.6L.

Absorption

The absorption of pantoprazole is rapid, with a C_{max} of 2.5 g/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0–23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g. 3% of Caucasians and African-Americans and 17–23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 23%) with once daily dosing.

Elimination

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric

Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (Also see Use in Women).

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7–9 hours and AUC values increased by 5- to 7- fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment.

Drug-Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Pharmacodynamics

Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+,K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20–80 mg) or a single dose of intravenous (20–120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one doubleblind crossover study are shown below.

[See first table above]

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20 and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups.

In long term studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials. Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors.

However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See **PRECAUTIONS**, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

Clinical Studies

PROTONIX Delayed-Release Tablets were used in all clinical trials.

Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

A US multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n=541) in this study were as follows:

[See second table above]

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 20-mg and 40-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 20 mg and 40 mg once daily were also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n=212) were as follows:

[See first table at top of next page]

Once daily treatment with PROTONIX 20 or 40 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

INDICATIONS AND USAGE

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

PROTONIX Delayed-Release Tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and

Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

Time	Median pH on day 7			
	Placebo	20 mg	40 mg	80 mg
8 a.m. – 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. – 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. – 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

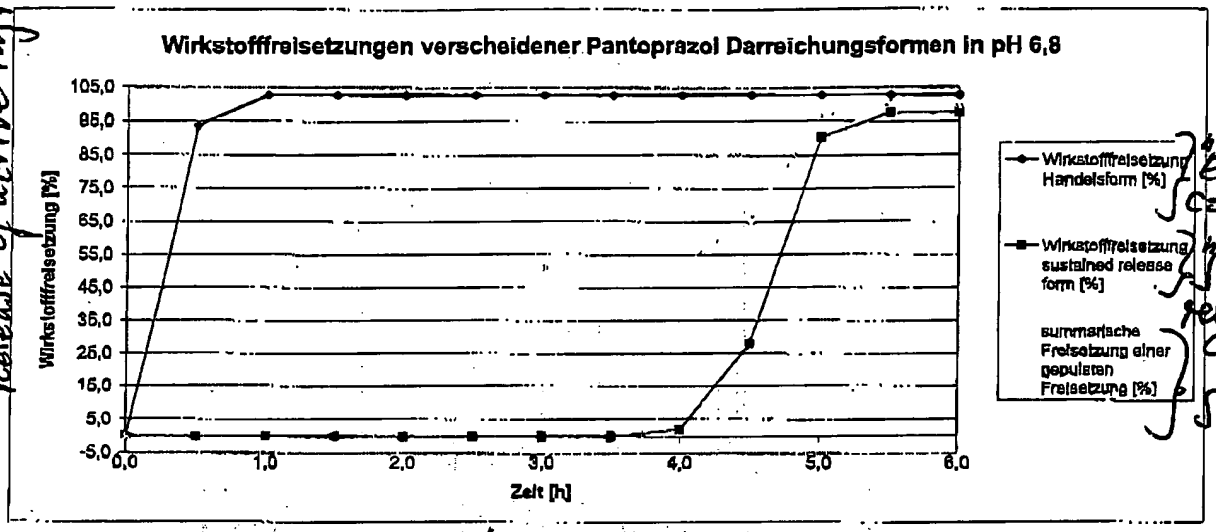
* Significantly different from placebo
\# Significantly different from 20 mg

Erosive Esophagitis Healing Rates (per protocol)

Week	PROTONIX 10 mg QD (n = 153)	PROTONIX 20 mg QD (n = 158)	PROTONIX 40 mg QD (n = 162)	Placebo (n = 68)
4	45.6%+	58.4%+#	75.0%+*	14.3%
8	66.0%+	83.5%+#	92.6%+*	39.7%

\+ ($p < 0.001$) PROTONIX versus placebo.
* ($p < 0.05$) versus 10 mg, or 20 mg PROTONIX
\# ($p < 0.05$) versus 10 mg PROTONIX

Zeit [h]	Wirkstofffreisetzung Handelsform [%]	Wirkstofffreisetzung sustained release form [%]	summarische Freisetzung einer gepulsten Freisetzung [%]
0,0	0,0	0,0	0,0
0,5	83,7	0,0	46,9
1,0	102,8	0,0	51,4
1,5	102,8	0,0	51,4
2,0	102,8	0,0	51,4
2,5	102,8	0,0	51,4
3,0	102,8	0,0	51,4
3,5	102,8	0,0	51,4
4,0	102,8	2,0	52,4
4,5	102,8	28,1	65,5
5,0	102,8	80,3	96,6
5,5	102,8	97,6	100,2
6,0	102,8	97,5	100,2



Release of active ingredient

"Enteric coating"

"Sustained release coating"

Sum

time